

Applicant : Ethan Lerner and Seishiro Fujii
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REMARKS

Upon entry of the amendment herein, claims 1, 2, 4, 5, 7, 8, 10, 11, 18, 21, and 22 will be pending. Claims 1, 7, and 18 have been amended. Claims 3, 6, 9, 12-17, 19-20, and 23-27 are or have been canceled without prejudice.

Claims 1, 2, 4, 5, 7, 10 and 11 stand rejected as allegedly unpatentable over WO 98/33379 (Lerner) in view of U.S. Pat. No. 6,037,481 (Zucchetti); claims 2 and 8 are rejected over Lerner in view of EP 0755671A1 (Yamaguchi); claims 18, 19, 21, and 22 stand rejected as allegedly unpatentable over Lerner in view of Zucchetti and in further view of Remington's Pharmaceutical Sciences, 17th ed. (Remington). The Lerner reference is at the core of all three rejections. The threshold issue is whether the Lerner reference provides any motivation to use a NOS inhibitor to treat wrinkles or, as currently recited, fine wrinkles.

The Examiner cites the following text from Lerner:

a method of treating a subject...for sunburn or other exposure to ultra-violet light, or for unwanted effects of aging in the skin. The method includes administering to the subject a treatment which decreases the level of nitric oxide (NO) in the skin. Lerner, page 4, lines 1-3.

The Examiner seizes on this language and argues on page 2-4 of the most recent action that "this teaching would motivate one of ordinary skill in the art to employ an inhibitor of NOS . . . to treat any unwanted effects of aging . . ." The Applicants respectfully disagree.

Clearly Lerner teaches that some effects of aging can be treated by decreasing the level of nitric oxide in the skin. However, it is not inevitable that Lerner teaches that each and every effect of aging or exposure to UV light can be treated in this manner. To determine the extent of Lerner's teaching, the reference must be considered as a whole. MPEP § 2141.03 instructs:

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. [emphasis added]

In this regard, Lerner also teaches, at page 2, lines 22-24, that:

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Conditions characterized by the lack of or by an insufficient number of dermal or epidermal cells, e.g., melanocytes or keratinocytes, or a lack of pigmentation, are treated by reducing the level of NO in the skin.

This passage tends to lead away from the use of a NOS inhibitor to treat wrinkles or fine wrinkles, since these are not fundamentally a defect in the number of melanocytes or keratinocytes. A wrinkle is a configuration change in the surface of the skin, without specific structural alterations at the histological level. Zucchetti suggests, at column 2, lines 42-47, that wrinkles may be due to deterioration of structural proteins such as collagen. For example, Zucchetti attributes this "to the drop in production of collagen, elastin and glucosaminoglycans." Neither Zucchetti nor Lerner suggests that this type of defect can be treated by decreasing nitric oxide, by increasing proliferation of melanocytes and keratinocytes, or by altering pigmentation. Yamaguchi, teaches (i) the formation of some wrinkles are accelerated by exposure to UV-B and (ii) wrinkles can be treated with a furan derivative. Again, neither Yamaguchi nor Lerner suggest that wrinkles can be treated by decreasing nitric oxide, by increasing proliferation of melanocytes and keratinocytes, or by altering pigmentation.

Even so, the Examiner's response focuses on the broader language in Lerner and fails to account for Lerner's scientific explanation about how NOS inhibitors modulate melanocyte and keatinocyte proliferation. For example, at pages 2-3 of the most recent action, the Examiner states:

Applicants' argue that Lerner teaches treating a subset of conditions associated with aging, i.e. conditions characterized by melanocytes or keratinocytes and neither Lerner nor Zucchetti teach or suggest that wrinkles are in any way associated with unwanted proliferation or insufficient number of melanocytes or keratinocytes. This is not persuasive because Lerner et al on page 4, first full paragraph, teach a method of treating a subject for sunburn or other exposure to ultraviolet light or for unwanted effects of aging on the skin by administering a treatment which decreases the level of nitric oxide (NO) in the skin.

Obviousness does not permit the Examiner to disregard the scientific explanation in Lerner. The Examiner merely resorts to broader language that fails to explicitly teach treating wrinkles. As a matter of law, the Examiner is required to find some support for the premise that Lerner's teachings as a whole would lead one to use a NOS inhibitor to treat wrinkles. In re

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Fine, 837 F2d 1071 (Fed. Cir. 1988), sets forth the basic standard. According to MPEP § 2143.01:

In *In re Fine*, the claims were directed to a system for detecting and measuring minute quantities on nitrogen compounds comprising a gas chromatograph, a converter which converts nitrogen compounds into nitric oxide by combustion, and a nitric oxide detector. The primary reference disclosed a system for monitoring sulfur compounds comprising a chromatograph, combustion means, and a detector, and the secondary reference taught nitric oxide detectors. The examiner and Board asserted that it would have been within the skill of the art to substitute one type of detector for another in the system of the primary reference, however the court found there was no support or explanation of this conclusion and reversed. [emphasis added]

The situation in *In re Fine* is not unlike the Examiner's obviousness rejection. Again, in *In re Fine*, the first reference disclosed a genus (detectors); and the second reference identified a species (a specific detector). Absent from the rejection was support for inserting the specific detector into the system in the first reference. In the present rejection, one reference discloses treating unwanted effects of aging and UV exposure. A second reference identifies wrinkles as an effect of (i) aging or (ii) UV-B exposure. However, no basis is advanced for inserting wrinkles into the first reference. Moreover, here the first reference, by explaining that the therapeutic mechanism relates to proliferation of melanocytes and keratinocytes, does not admit to the modification. Thus, a prima facie case of obviousness has not been established.

In the Advisory Action mailed December 8, 2004, the Examiner states

Lerner teaches the treatment of 'epidermal or dermal condition' which refers to any unwanted conditions e.g. a disorder, or skin associated with aging, exposure to sun which would motivate one of ordinary skill in the art to employ an inhibitor of NO (L-NAME) as taught by Lerner to treat unwanted dermal condition such as skin aging (e.g. wrinkles).

However, there are many unrelated skin disorders associated with aging and exposure to sun. The issue is which, if any, specific skin disorders does Lerner point to. In context, however, Lerner points to those "[c]onditions characterized by an insufficient number of dermal or epidermal cells, e.g., melanocytes or keratinocytes, or a lack of pigmentation." Lerner, page 2. However, as discussed above, fine wrinkles do not appear from the face of Lerner to be such a condition. In other words, there is no suggestion in Lerner or in any other cited reference that

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fine wrinkles are characterized by an insufficient number of dermal or epidermal cells, e.g., melanocytes or keratinocytes, or a lack of pigmentation." Thus, contrary to the Examiner's assertion there is no suggestion in Lerner that L-NAME can be used to treat fine wrinkles, much less a reasonable basis for expecting that L-NAME would be effective for treating fine wrinkles.

A person of skill in the art, reading Lerner and Zucchetti or Lerner and Yamaguchi, would have no basis for thinking that L-NAME can be successfully used to treat wrinkles or fine wrinkles. As discussed above, Zucchetti characterizes wrinkles as a defect in collagen, elastin and glucosaminoglycans that can be treated with levogyre ascorbic acid (LAA). Yamaguchi characterizes UV-B accelerated wrinkles as a defect that can be treated by a furan derivative. Yamaguchi does not explain how furan derivatives treat wrinkles. Lerner characterizes the use of NOS inhibitors as increasing melanocytes or keratinocytes or altering pigmentation. These disparities between the references are evidence of a lack of expectation of success.

The burden is on the Examiner to establish a reasonable expectation of success. Results from completely unrelated compounds, such as LAA and furan derivatives cannot be used to support an expectation of success for the use of L-NAME. The results in Lerner also do not support an expectation of success because the results in Lerner were that L-NAME increased the number of melanocytes and keratinocytes and altered pigmentation. These results have no bearing on the treatment of fine wrinkles.

The Advisory Action mailed December 8, 2004 does not address this independent argument regarding the lack of expectation of success. In view of the absence of an expectation of success in the prior art and Applicants' surprisingly successful demonstration of L-NAME for the treatment of fine wrinkles, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the pending claims. Applicants respectfully submit that the claims are in condition for allowance.

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Respectfully submitted,

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24 Jan 2005

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